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(54) Title: COMBINATION THERAPY FOR THE TREATMENT OF NEOPLASMS

(57) Abstract: The invention features methods, kits, and compositions for the treatment of cancer and other proliferative diseases.

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COMBINATION THERAPY FOR THE TREATMENT OF NEOPLASMS

Background of the Invention

The present invention relates to the treatment of cancer and other proliferative diseases.

Cancer is a disease marked by the uncontrolled growth of abnormal cells. Cancer cells have overcome the barriers imposed in normal cells, which have a finite lifespan, to grow indefinitely. As the growth of cancer cells continue, genetic alterations may persist until the cancerous cell has manifested itself to pursue a more aggressive growth phenotype. If left untreated, metastasis, the spread of cancer cells to distant areas of the body by way of the lymph system or bloodstream, may ensue, destroying healthy tissue.

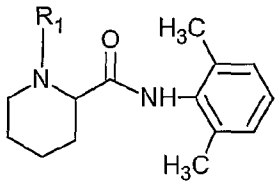
The treatment of cancer has been hampered by the fact that there is considerable heterogeneity even within one type of cancer. Some cancers, for example, have the ability to invade tissues and display an aggressive course of growth characterized by metastases. These tumors generally are associated with a poor outcome for the patient. Ultimately, tumor heterogeneity results in the phenomenon of multiple drug resistance, i.e., resistance to a wide range of structurally unrelated cytotoxic anticancer compounds, J. H. Gerlach et al., Cancer Surveys, 5:25-46 (1986). The underlying cause of progressive drug resistance may be due to a small population of drug-resistant cells within the tumor (e.g., mutant cells) at the time of diagnosis, as described, for example, by J. H. Goldie and Andrew J. Coldman, Cancer Research, 44:3643-3653 (1984). Treating such a tumor with a single drug can result in remission, where the tumor shrinks in size as a result of the killing of the predominant drug-sensitive cells. However, with the drug-sensitive cells gone, the remaining drug-resistant cells can continue to multiply and eventually dominate the cell population of the tumor. Therefore, the problems of why metastatic cancers

develop pleiotropic resistance to all available therapies, and how this might be countered, are the most pressing in cancer chemotherapy.

Anticancer therapeutic approaches are needed that are reliable for a wide variety of tumor types, and particularly suitable for invasive tumors. Importantly, the treatment must be effective with minimal host toxicity. In spite of the long history of using multiple drug combinations for the treatment of cancer and, in particular, the treatment of multiple drug resistant cancer, positive results obtained using combination therapy are still frequently unpredictable.

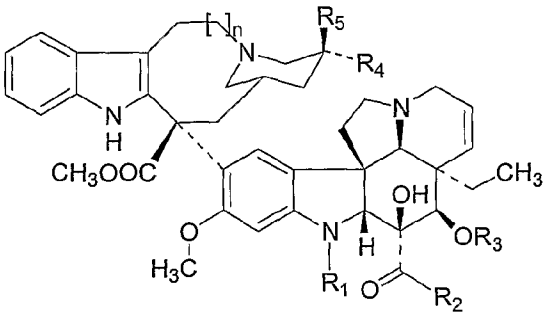
Summary of the Invention

We have discovered that dibucaine and amide local anaesthetics related to bupivacaine significantly enhance the antiproliferative activity of vinca alkaloids against cancer cells. This enhancement of the antiproliferative activity of vinca alkaloids by various amide local anaesthetics was measured using HCT116 colon adenocarcinoma cell line in a cell viability assay. Structural and functional analogs of these amide local anaesthetics are known and can be used in combination with derivatives of vinca alkaloids. Accordingly, the invention features a method for treating a patient who has a proliferative disease by administering to the patient a compound having formula (I):



(I)

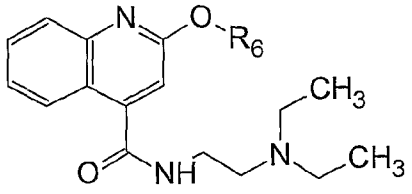
wherein R_1 is H, OH, a halide, or any branched or unbranched, substituted or unsubstituted C_{1-10} alkyl (preferably R_1 is CH_3-, $CH_3CH_2CH_2$-, or $CH_3CH_2CH_2CH_2$-), C_{1-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} aminoalkyl, C_{1-10} alkylaminoalkyl, C_{4-10} cycloalkyl, C_{5-8} aryl, or C_{6-20} alkylaryl; and a compound having formula (II):



(II)

wherein R_1 is CHO, CH_3, or H, R_2 is OCH_3 or NH_2, R_3 is $OCOCH_3$ or OH, R_4 is H, CH_3, CH_2CH_3, or CF_2CH_3, R_5 is H, OH, or CH_2CH_3, and n=0 or 1, wherein the compounds are administered simultaneously or within 21 days of each other in amounts sufficient to treat the patient.

The invention also features a method for treating a patient who has a proliferative disease by administering to the patient a compound having formula (III):



(III)

where R_6 is $-((CH)_2)_2$-O-CH_3; $-((CH)_2)_2$-O-CH_2-CH_3; or $-((CH)_2)_3CH_3$; and a compound of formula (II), wherein the compounds are administered simultaneously or within 21 days of each other in amounts sufficient to treat the patient.

Suitable compounds of formula (I) include bupivacaine, levobupivacaine, ropivacaine, and mepivacaine. Suitable compounds of formula (II) include vinorelbine, vincristine, vindesine, vinblastine, and 3',4'-anhydrovinblastine. Suitable compounds of formula (III) include dibucaine.

Desirably, in either of the above aspects, the two agents are administered simultaneously or within 14 days of each other, within 7 days of each other, within 1 day of each other, within 1 hour of each other in amounts sufficient to treat the patient. Most desirably, the compounds are administered in the same pharmaceutical formulation, although the compounds can be administered by different routes. Routes of administration include intravenous, intramuscular,

subcutaneous, rectal, oral, topical, intravaginal, ophthalmic, or inhalation administration.

A compound of formula (I) or (III) is administered in an amount, frequency, and duration, which measurably enhances the effectiveness of a compound of formula (II). A compound of formula (I) or (III) is desirably administered in an amount between 0.01 and 2000 mg/day, 0.1 and 1000 mg/day, or 1.0 and 500 mg/day. Alternatively, a compound of formula (I) or (III) can be administered as a 0.5% to 25% w/v topical formulation. Such topical formulations are particularly useful for treating cancers of the skin and glands of the dermis and epidermis (i.e., sweat glands and sebaceous glands).

The compounds can be provided together in a pharmaceutical composition that contains a pharmaceutically acceptable carrier. When formulated for single dose delivery, a compound of formula (I) or (III) is desirably present in the composition in an amount between 1.0 and 2000 mg, more desirably between 10 and 1000 mg. Of course, bulk preparations suitable for reformulating into single doses may contain higher amounts. The preferred ratio of molar concentrations of a compound of formula (I) or (III) to a compound of formula (II) is approximately 2000:1. Compounds employed in the methods of the invention can be provided as components of a pharmaceutical pack. Such a pack would typically also include instructions for using the compounds in the methods of the invention. In these packs, compounds can be formulated together or separately and in individual dosage amounts.

The invention also features a method for treating a patient having a proliferative disease in which one of the foregoing methods is performed in combination with an additional treatment for cancer, such as surgery, radiation therapy, chemotherapy, immunotherapy, anti-angiogenesis therapy, or gene therapy. The two treatments are typically within six months of each other, and may be performed concurrently. Preferably, the additional treatment is chemotherapy. Most preferably, the additional treatment includes administering to a patient cisplatin, daunorubicin, doxorubicin, etoposide,

methotrexate, mercaptopurine, fluorouracil, hydroxyurea, vinblastine, vincristine, paclitaxel, or any combination thereof.

Cancers treated according to any of the methods of the invention can be, for example, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (Hodgkin's disease, non-Hodgkin's disease), Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma. Preferably, the cancer being treated is lung cancer, especially lung cancer attributed to squamous cell carcinoma, adenocarinoma, or large cell carcinoma, colorectal cancer, ovarian cancer, especially ovarian adenocarcinoma, or prostate cancer.

In particular embodiments of this invention, a compound of formula (I) or (III) is administered in combination with a compound of formula (II) and one, two, three, or more additional antiproliferative agents, in amounts and

frequencies sufficient to inhibit growth of the neoplasm. Typically, each is administered at least once during a 28-day period, and may, independently, be administered twice, three times, four times, or even daily (28 times) during a 28 day period, as required to inhibit growth of the neoplasm.

By "cancer" or "neoplasm" or "neoplastic cells" is meant a collection of cells multiplying in an abnormal manner. Cancer growth is uncontrolled and progressive, and occurs under conditions that would not elicit, or would cause cessation of, multiplication of normal cells.

By "more effective" is meant that a method, composition, or kit exhibits greater efficacy, is less toxic, safer, more convenient, better tolerated, or less expensive, or provides more treatment satisfaction than another method, composition, or kit with which it is being compared. Efficacy may be measured by a skilled practitioner using any standard method that is appropriate for a given indication.

By a "vinca alkaloid" is meant a compound of formula (II), which encompasses plant-derived antiproliferative compound such as vinblastine, vinleurosine, vinrosidine or vincristine (each found in the Madagascar periwinkle, *Catharanthus roseus*) as well as the semi-synthetic derivatives such as vindesine and vinorelbine.

By an "antiproliferative agent" is meant a compound that, individually, inhibits the growth of a neoplasm. Antiproliferative agents include, but are not limited to microtubule inhibitors, topoisomerase inhibitors, platins, alkylating agents, and anti-metabolites. Particular antiproliferative agents include paclitaxel, gemcitabine, doxorubicin, vinblastine, etoposide, 5-fluorouracil, carboplatin, altretamine, aminoglutethimide, amsacrine, anastrozole, azacitidine, bleomycin, busulfan, carmustine, chlorambucil, 2-chlorodeoxyadenosine, cisplatin, colchicine, cyclophosphamide, cytarabine, cytoxan, dacarbazine, dactinomycin, daunorubicin, docetaxel, estramustine phosphate, floxuridine, fludarabine, gentuzumab, hexamethylmelamine, hydroxyurea, ifosfamide, imatinib, interferon, irinotecan, lomustine, mechlorethamine, melphalen, 6-mercaptopurine, methotrexate, mitomycin,

mitotane, mitoxantrone, pentostatin, procarbazine, rituximab, streptozocin, tamoxifen, temozolomide, teniposide, 6-thioguanine, topotecan, trastuzumab, vincristine, vindesine, and vinorelbine.

By "inhibits cell proliferation" is meant measurably slows, stops, or reverses the growth rate of cells *in vitro* or *in vivo*. Desirably, a slowing of the growth rate is by at least 20%, 30%, 50%, 60%, 70%, 80%, or 90%, as determined using a suitable assay for determination of cell growth rates (e.g., a cell growth assay described herein). Typically, a reversal of growth rate is accomplished by initiating or accelerating necrotic or apoptotic mechanisms of cell death in the proliferating cells.

By "a sufficient amount" is meant the amount of a compound, in a combination according to the invention, required to inhibit the growth of the cells of a neoplasm *in vivo*. The effective amount of active compound(s) used to practice the present invention for therapeutic treatment of proliferative diseases (i.e., cancer) varies depending upon the manner of administration, the age, race, gender, organ affected, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen.

The combination of a compound of formula (I) or (III) with a compound of formula (II) for the treatment of proliferative diseases allows for the administration of lower doses of each compound, providing similar efficacy or increased efficacy, compared to administration of either compound alone. The methods also allow for the administration of standard doses of each compound, providing improved efficacy, compared to the administration of either compound alone.

By a "low dosage" is meant at least 5% less (e.g., at least 10%, 20%, 50%, 80%, 90%, or even 95%) than the lowest standard recommended dosage of a particular compound formulated for a given route of administration for treatment of any human disease or condition.

By a "high dosage" is meant at least 5% (e.g., at least 10%, 20%, 50%, 100%, 200%, or even 300%) more than the highest standard recommended

dosage of a particular compound for treatment of any human disease or condition.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to patient.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art.

By "patient" is meant any animal (e.g., a human). Non-human animals that can be treated using the methods, compositions, and kits of the invention include horses, dogs, cats, pigs, goats, rabbits, hamsters, monkeys, guinea pigs, rats, mice, lizards, snakes, sheep, cattle, fish, and birds.

Compounds useful in the invention include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, thereof, as well as racemic mixtures of the compounds described herein.

As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e., cycloalkyl groups. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 20 ring carbon atoms, inclusive. Exemplary cyclic groups include cyclopropyl, cyclopentyl, cyclohexyl, and adamantyl groups.

By "aromatic residue" is meant an aromatic group having a ring system with conjugated π electrons (e.g., phenyl, or imidazole). The ring of the aryl group is preferably 5 to 10 atoms. The aromatic ring may be exclusively composed of carbon atoms or may be composed of a mixture of carbon atoms and heteroatoms. Preferred heteroatoms include nitrogen, oxygen, sulfur, and phosphorous. Aryl groups may optionally include monocyclic, bicyclic, or tricyclic rings, where each ring has preferably five or six members. The aryl group may be substituted or unsubstituted. Exemplary substituents include alkyl, hydroxyl, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halogen,

fluoroalkyl, carboxyl, carboxyalkyl, amino, aminoalkyl, monosubstituted amino, disubstituted amino, and quaternary amino groups.

The term "aryl" means carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl, and indenyl groups. The term "heteroaryl" means aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Aryl groups may be unsubstituted or substituted by one or more substituents selected from the group consisting of C_{1-10} alkyl, hydroxy, halo, nitro, C_{1-10} alkoxy, C_{1-10} alkylthio, trihalomethyl, C_{1-10} acyl, arylcarbonyl, nitrile, C_{1-10} alkoxycarbonyl, oxo, and arylalkyl (wherein the alkyl group has from 1 to 10 carbon atoms).

By "treating" is meant administering or prescribing a pharmaceutical composition for the treatment or prevention of an inflammatory disease.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Detailed Description

The invention features compositions, methods, and kits for treating proliferative diseases.

Normal cells have signaling mechanisms that regulate growth, mitosis, differentiation, cell function, and cell death in a programmed fashion. Defects in the signaling pathways that regulate these functions can result in uncontrolled growth and proliferation, which can manifest as cancer, hyperplasias, restenosis, cardiac hypertrophy, immune disorders and inflammatory disorders.

We have discovered that compounds of formula (I) or formula (III) enhance the activity of antiproliferative vinca alkaloids (compounds of formula (II)) against cancer cells *in vitro*. Thus, a compound of formula (I) or (III) is useful in combination with a compound of formula (II) for the treatment of cancer and other proliferative diseases.

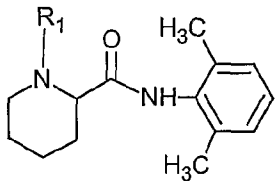
Vinblastine, either alone or in combination with known anesthetic agents, was assessed for antiproliferative activity against human colorectal

carcinoma HCT116. Alamar Blue dye was used to measure the metabolic potential of the tumor cells and can be taken as an indirect measure of the number of viable cells remaining after the treatment period. Alamar Blue dye is a blue non-fluorescent dye that is reduced, by living cells, to a red fluorescent product that can be easily quantified.

In the examples provided herein, tumor cells were treated with a combination of vinblastine and one of the following compounds: bupivacaine, levobupivacaine, mepivacaine, and dibucaine. In each of these combinations, vinblastine efficacy as an antiproliferative agent is enhanced.

Compounds of Formula (I)

Compounds of formula (I) have the formula:



(I)

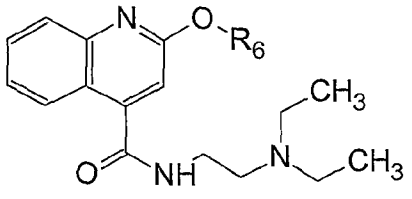
wherein R_1 is H, OH, a halide, or any branched or unbranched, substituted or unsubstituted C_{1-10} alkyl, C_{1-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} aminoalkyl, C_{1-10} alkylaminoalkyl, C_{4-10} cycloalkyl, C_{5-8} aryl, or C_{6-20} alkylaryl; most preferably R_1 is CH_3-, $CH_3CH_2CH_2$-, or $CH_3CH_2CH_2CH_2$-.

Exemplary compounds of this formula are bupivacaine (1-butyl-2',6'-pipecoloxylidide), levobupivacaine (also called chirocaine; (S)-1-butyl-2',6'-pipecoloxylidide), mepivacaine ((+/-)-1-methyl-2',6'-pipecoloxylidide), and ropivacaine ((-)-1-propyl-2',6'-pipecoloxylidide). These compounds are tertiary amide local anaesthetics. Local anaesthetics block the initiation and propagation of action potentials by preventing the voltage-dependent increase in Na^+ conductance. They can be used for surgical anesthesia and postoperative pain management. For surgical anesthesia, bupivacaine has been approved for epidural use, peripheral neural blockade, and local infiltration as well as for pain management. Typically, a 0.75% solution of bupivacaine is administered

for ophthalmic surgery. A 0.5% bupivacaine solution may be administered for Cesarean section or peripheral nerve block. A 0.25% solution of bupivacaine may be administered in infiltration anaesthesia or to women in early labor requesting epidural analgesia. A composition of 0.125% bupivacaine may be used for postoperative pain management. Levobupivacaine and ropivacaine have similar administration, while mepivacaine is ineffective as a topical anaesthetic.

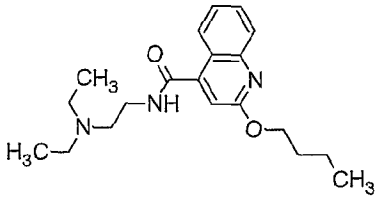
Compounds of Formula (III)

Compounds of formula (III) have the formula:



(III)

wherein R_6 is $-((CH)_2)_2OCH_3$, $-((CH)_2)_2OCH_2CH_3$, or $-((CH)_2)_3CH_3$. An exemplary member of this class is dibucaine (2-butoxy-N-(2-(diethylamino)ethyl)cinchoninamide), which has the formula (IV):



(IV).

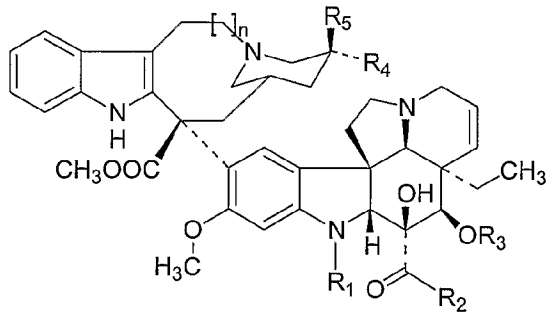
Dibucaine (2-butoxy-N-(2-(diethylamino)ethyl)cinchoninamide) is used as a topical analgesic, anaesthetic and antipruritic for the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites and minor skin irritations. It is typically formulated as a 0.5% to 1% solution.

Compounds of Formula (II)

Compounds of formula (II) are vinca alkaloids, antineoplastic agents that act by binding tubulin and inhibiting its polymerization into microtubules. Examples of vinca alkaloids are vinblastine, vinorelbine, vindesine, and

vincristine. Vinblastine is usually administered in a weekly dose 0.3 mg/kg. If the patient does not exhibit a moderate amount of leukopenia, the dose may be increased each week by 0.05 mg/kg of body weight. Vincristine is typically intravenously administered at a weekly dose of 2 mg/m^2 of body surface area. For adult patients with Hodgkin's disease or non-Hodgkin's lymphomas, vincristine is typically administered at a weekly dose of 1.4 mg/m^2. Vinorelbine is primarily used in breast cancer and small-cell lung cancer. It is generally administered to patients every week intravenously at 30 mg/m^2, but has been given as an oral capsule in experimental studies.

Compounds of formula (II) have the formula:



(II)

wherein R_1 is CHO, CH_3, or H, R_2 is OCH_3 or NH_2, R_3 is $OCOCH_3$ or OH, R_4 is H, CH_3, CH_2CH_3, or CF_2CH_3, R_5 is H, OH, or CH_2CH_3, and n=0 or 1.

Formulation of Pharmaceutical Compositions

Suitable modes of administration include oral, rectal, intravenous, intramuscular, subcutaneous, inhalation, topical or transdermal, vaginal, intraperitoneal (IP), intraarticular, and ophthalmic.

Administration of a compound may be by any suitable means that is effective for the treatment of an immunoinflammatory disorder, proliferative skin disease, organ transplant rejection, or graft versus host disease. Compounds are admixed with a suitable carrier substance, and are generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for oral, parenteral (e.g., intravenous, intramuscular, subcutaneous), rectal, transdermal, nasal, vaginal, inhalant, or ocular administration. Thus, the

composition may be in form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy, (20th ed.) ed. A.R. Gennaro, 2000, Lippincott Williams & Wilkins, Philedelphia, PA. and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-2002, Marcel Dekker, New York).

Therapy

The compounds of the invention are useful for the treatment of cancers and other proliferative diseases. Therapy may be performed alone or in conjunction with another therapy (e.g., surgery, radiation therapy, chemotherapy, immunotherapy, anti-angiogenesis therapy, or gene therapy). Additionally, a person having a greater risk of developing a neoplasm or other proliferative disease (e.g., one who is genetically predisposed or one who previously had such a disorder) may receive prophylactic treatment to inhibit or delay hyperproliferation. The duration of the combination therapy depends on the type of disease or disorder being treated, the age and condition of the patient, the stage and type of the patient's disease, and how the patient responds to the treatment. Therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to recovery from any as yet unforeseen side-effects. Desirably, the methods, compositions, and kits of the invention are more effective than other methods, compositions, and kits. By "more effective" is meant that a method, composition, or kit exhibits greater efficacy, is less toxic, safer, more convenient, better tolerated, or less expensive, or provides more treatment satisfaction than another method, composition, or kit with which it is being compared.

Cancers include, without limitation, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic

leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (Hodgkin's disease, non-Hodgkin's disease), Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

Other proliferative diseases that can be treated with the combinations and methods of the invention include lymphoproliferative diseases and psoriasis. By "lymphoproliferative disease" is meant a disorder in which there is abnormal proliferation of cells of the lymphatic system (e.g., T-cells and B-cells), and includes multiple sclerosis, Crohn's disease, lupus erythematosus, rheumatoid arthritis, and osteoarthritis.

Additionally therapy can include the use of other antiproliferative agents with the combinations of the invention. For example, when treatment is for cancer, the combination may be administered with an anticancer agent, such as the agents in Table 1, below.

Table 1

Alkylating agents	Busulfan dacarbazine ifosfamide hexamethylmelamine thiotepa dacarbazine lomustine cyclophosphamide chlorambucil	procarbazine altretamine estramustine phosphate mechlorethamine streptozocin temozolomide Semustine cisplatin
Platinum agents	spiroplatin tetraplatin ormaplatin iproplatin ZD-0473 (AnorMED) oxaliplatin carboplatin	lobaplatin (Aeterna) satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
Antimetabolites	azacytidine Floxuridine 2-chlorodeoxyadenosine 6-mercaptopurine 6-thioguanine cytarabine 2-fluorodeoxy cytidine methotrexate tomudex fludarabine raltitrexed	trimetrexate deoxycoformycin pentostatin hydroxyurea decitabine (SuperGen) clofarabine (Bioenvision) irofulven (MGI Pharma) DMDC (Hoffmann-La Roche) ethynylcytidine (Taiho) gemcitabine capecitabine

Table 1 (cont.)

Topoisomerase inhibitors	amsacrine epirubicin etoposide teniposide or mitoxantrone 7-ethyl-10-hydroxy-camptothecin dexrazoxanet (TopoTarget) pixantrone (Novuspharma) rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharma) rubitecan (SuperGen) irinotecan (CPT-11) topotecan	exatecan mesylate (Daiichi) quinamed (ChemGenex) gimatecan (Sigma-Tau) diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko) hydroxycamptothecin (SN-38)
Antitumor antibiotics	dactinomycin (actinomycin D) valrubicin daunorubicin (daunomycin) therarubicin idarubicin rubidazone plicamycin porfiromycin mitoxantrone (novantrone) amonafide	azonafide anthrapyrazole oxantrazole losoxantrone bleomycinic acid MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals) epirubicin mitoxantrone
Antimitotic agents	colchicine vinblastine vindesine dolastatin 10 (NCI) rhizoxin (Fujisawa) mivobulin (Warner-Lambert) cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) cryptophycin 52 (Eli Lilly) vinflunine (Fabre) auristatin PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) taxoprexin (Protarga) SB 408075 (GlaxoSmithKline) vinorelbine	E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTAMedica) ER-86526 (Eisai) combretastatin A4 (BMS) isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroPharma) azaepothilone B (BMS) BNP-7787 (BioNumerik) CA-4 prodrug (OXiGENE) dolastatin-10 (NIH) CA-4 (OXiGENE) docetaxel vincristine paclitaxel
Aromatase inhibitors	aminoglutethimide atamestane (BioMedicines) letrozole anastrazole	YM-511 (Yamanouchi) formestane exemestane

Table 1 (cont.)

Thymidylate synthase inhibitors	pemetrexed (Eli Lilly) ZD-9331 (BTG)	nolatrexed (Eximias) CoFactor™ (BioKeys)
DNA antagonists	trabectedin (PharmaMar) glufosfamide (Baxter International) albumin + 32P (Isotope Solutions) thymectacin (NewBiotics)	edotreotide (Novartis) mafosfamide (Baxter International) apaziquone (Spectrum Pharmaceuticals) O6 benzyl guanine (Paligent)
Farnesyltransferase inhibitors	arglabin (NuOncology Labs) lonafarnib (Schering-Plough) BAY-43-9006 (Bayer)	tipifarnib (Johnson & Johnson) perillyl alcohol (DOR BioPharma)
Pump inhibitors	CBT-1 (CBA Pharma) tariquidar (Xenova) MS-209 (Schering AG)	zosuquidar trihydrochloride (Eli Lilly) biricodar dicitrate (Vertex)
Histone acetyltransferase inhibitors	tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	pivaloyloxymethyl butyrate (Titan) depsipeptide (Fujisawa)
Metalloproteinase inhibitors	Neovastat (Aeterna Laboratories) marimastat (British Biotech)	CMT-3 (CollaGenex) BMS-275291 (Celltech)
Ribonucleoside reductase inhibitors	gallium maltolate (Titan) triapine (Vion)	tezacitabine (Aventis) didox (Molecules for Health)
TNF alpha agonists/antagonists	virulizin (Lorus Therapeutics) CDC-394 (Celgene)	revimid (Celgene)
Endothelin A receptor antagonist	atrasentan (Abbott) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
Retinoic acid receptor agonists	fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	alitretinoin (Ligand)
Immuno-modulators	interferon oncophage (Antigenics) GMK (Progenics) adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) IRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) synchrovax vaccines (CTL Immuno) melanoma vaccine (CTL Immuno) p21 RAS vaccine (GemVax)	dexosome therapy (Anosys) pentrix (Australian Cancer Technology) ISF-154 (Tragen) cancer vaccine (Intercell) norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) ß-alethine (Dovetail) CLL therapy (Vasogen)

Table 1 (cont.)

Hormonal and antihormonal agents	estrogens conjugated estrogens ethinyl estradiol chlortrianisen idenestrol hydroxyprogesterone caproate medroxyprogesterone testosterone testosterone propionate fluoxymesterone methyltestosterone diethylstilbestrol megestrol bicalutamide flutamide nilutamide	dexamethasone prednisone methylprednisolone prednisolone aminoglutethimide leuprolide octreotide mitotane P-04 (Novogen) 2-methoxyestradiol (EntreMed) arzoxifene (Eli Lilly) tamoxifen toremofine goserelin leuporelin bicalutamide
Photodynamic agents	talaporfin (Light Sciences) Theralux (Theratechnologies) motexafin gadolinium (Pharmacyclics)	Pd-bacteriopheophorbide (Yeda) lutetium texaphyrin (Pharmacyclics) hypericin
Kinase Inhibitors	imatinib (Novartis) leflunomide (Sugen/Pharmacia) ZD1839 (AstraZeneca) erlotinib (Oncogene Science) canertinib (Pfizer) squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline) EKB-509 (Wyeth) trastuzumab (Genentech)	EKB-569 (Wyeth) kahalide F (PharmaMar) CEP-701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol (Novogen) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone) Tyrphostins Gefitinib (Iressa)

Table 1 (cont.)

Miscellaneous agents	
SR-27897 (CCK A inhibitor, Sanofi-Synthelabo)	ceflatonin (apoptosis promotor, ChemGenex)
tocladesine (cyclic AMP agonist, Ribapharm)	BCX-1777 (PNP inhibitor, BioCryst)
alvocidib (CDK inhibitor, Aventis)	ranpirnase (ribonuclease stimulant, Alfacell)
CV-247 (COX-2 inhibitor, Ivy Medical)	galarubicin (RNA synthesis inhibitor, Dong-A)
P54 (COX-2 inhibitor, Phytopharm)	tirapazamine (reducing agent, SRI International)
CapCell™ (CYP450 stimulant, Bavarian Nordic)	N-acetylcysteine (reducing agent, Zambon)
GCS-100 (gal3 antagonist, GlycoGenesys)	R-flurbiprofen (NF-kappaB inhibitor, Encore)
G17DT immunogen (gastrin inhibitor, Aphton)	3CPA (NF-kappaB inhibitor, Active Biotech)
efaproxiral (oxygenator, Allos Therapeutics)	seocalcitol (vitamin D receptor agonist, Leo)
PI-88 (heparanase inhibitor, Progen)	131-I-TM-601 (DNA antagonist, TransMolecular)
tesmilifene (histamine antagonist, YM BioSciences)	eflornithine (ODC inhibitor , ILEX Oncology)
histamine (histamine H2 receptor agonist, Maxim)	minodronic acid (osteoclast inhibitor, Yamanouchi)
tiazofurin (IMPDH inhibitor, Ribapharm)	indisulam (p53 stimulant, Eisai)
cilengitide (integrin antagonist, Merck KGaA)	aplidine (PPT inhibitor, PharmaMar)
SR-31747 (IL-1 antagonist, Sanofi-Synthelabo)	gemtuzumab (CD33 antibody, Wyeth Ayerst)
CCI-779 (mTOR kinase inhibitor, Wyeth)	PG2 (hematopoiesis enhancer, Pharmagenesis)
exisulind (PDE V inhibitor, Cell Pathways)	Immunol™ (triclosan oral rinse, Endo)
CP-461 (PDE V inhibitor, Cell Pathways)	triacetyluridine (uridine prodrug , Wellstat)
AG-2037 (GART inhibitor, Pfizer)	SN-4071 (sarcoma agent, Signature BioScience)
WX-UK1 (plasminogen activator inhibitor, Wilex)	TransMID-107™ (immunotoxin, KS Biomedix)
PBI-1402 (PMN stimulant, ProMetic LifeSciences)	PCK-3145 (apoptosis promotor, Procyon)
bortezomib (proteasome inhibitor, Millennium)	doranidazole (apoptosis promotor, Pola)
SRL-172 (T cell stimulant, SR Pharma)	CHS-828 (cytotoxic agent, Leo)
TLK-286 (glutathione S transferase inhibitor, Telik)	trans-retinoic acid (differentiator, NIH)
PT-100 (growth factor agonist, Point Therapeutics)	MX6 (apoptosis promotor, MAXIA)
midostaurin (PKC inhibitor, Novartis)	apomine (apoptosis promotor, ILEX Oncology)
bryostatin-1 (PKC stimulant, GPC Biotech)	urocidin (apoptosis promotor, Bioniche)
CDA-II (apoptosis promotor, Everlife)	Ro-31-7453 (apoptosis promotor, La Roche)
SDX-101 (apoptosis promotor, Salmedix)	brostallicin (apoptosis promotor, Pharmacia)
rituximab (CD20 antibody, Genentech	

Dosages

The dosage of each compound of the claimed combinations depends on several factors, including: the administration method, the neoplasm to be treated, the severity of the neoplasm, whether the neoplasm is to be treated or prevented, and the age, weight, and health of the patient to be treated.

A compound of the combination may be administered orally in the form of tablets, capsules, elixirs or syrups, or rectally in the form of suppositories. Parenteral administration of a compound is suitably performed, for example, in the form of saline solutions or with the compound incorporated into liposomes. In cases where the compound in itself is not sufficiently soluble to be

dissolved, a solubilizer such as ethanol can be applied. One skilled in the art will recognize that if an alternative compound is substituted for either a bupivacaine analog or dibucaine analog or any one of the antiproliferative agents, the correct dosage can be determined by examining the efficacy of the compound in cell proliferation assays. For topical administration, a compound of formula (I) or formula (III) is usually provided in a 0.1%-25% w/v solution, cream, or gel. A compound of formula (II) is usually given by the same routes of administration that are known to be effective for delivering such a compound. When used in combination therapy according to the methods of this invention, a compound of formula (II) is dosed in an amount and frequency equivalent to or less than those that result in effective anticancer monotherapy using that compound.

The following examples are to illustrate the invention and are not intended to be limiting in any way.

Example 1: Antiproliferative Activity of Bupivacaine and Vinblastine Against Human Colorectal Carcinoma HCT116

The results from a 2-fold dilution series of viblastine and bupivacaine combination on HCT116 cell growth are shown in Table 2. In the present assay, the IC_{50} of vinblastine alone is approximately 0.8 nM. However, in the presence of 6.16 μM bupivacaine, the efficacy of vinblastine is enhanced, having an IC_{50} at approximately 0.4 nM; a 2-fold reduction of vinblastine. The data also demonstrate that, in this assay, vinblastine maximally inhibits neoplastic cell proliferation by about 85% at concentrations of 25 nM. The addition of 1.54 μM bupivacaine reduces the vinblastine concentration required for maximal growth inhibition to 0.8 nM, more than a 30-fold reduction.

Table 2. Percent inhibition of Alamar Blue incorporation in HCT116 cells											
		[Bupivacaine] (μM)									
[Vinblastine] (μM)		6.160	3.080	1.540	0.770	0.385	0.193	0.096	0.048	0.024	0.000
	0.0250	85.57	84.89	83.56	83.08	84.15	83.90	83.89	84.26	83.82	83.90
	0.0125	83.89	84.38	84.30	83.40	83.78	82.63	83.26	80.23	80.16	81.03
	0.0063	88.46	87.34	89.20	81.51	86.90	87.99	82.37	87.18	84.34	76.26
	0.0031	87.77	87.54	84.65	84.41	82.50	84.14	84.69	81.77	80.45	74.21
	0.0016	83.74	86.93	90.10	80.82	77.53	82.44	68.13	72.82	63.89	56.70
	0.0008	76.26	77.88	82.15	76.43	77.99	42.40	51.51	36.36	30.86	47.51
	0.0004	43.95	39.67	19.09	44.19	22.35	25.52	14.61	4.72	1.52	5.48
	0.0002	38.75	43.82	24.95	17.43	36.29	26.41	13.26	2.78	6.96	8.47
	0.0001	14.20	14.05	4.55	21.92	4.45	14.50	9.18	1.31	10.61	0.47
	0.0000	23.41	19.65	10.97	19.38	21.04	13.27	20.09	7.08	12.15	13.69

Example 2: Antiproliferative Activity of Levobupivacaine and Vinblastine Against Human Colorectal Carcinoma HCT116

The results from a 2-fold dilution series of vinblastine and levobupivacaine combination on HCT116 cell growth are shown in Table 3. In the present assay, the IC_{50} of vinblastine alone is approximately 1.6 nM. Vinblastine alone, at a concentration of at least 25 nM, maximally inhibits HCT116 cell proliferation by about 83%. In the presence of 3.08 μM levobupivacaine, maximal vinblastine inhibition is observed at concentrations as low as 1.6 nM, nearly a 16-fold reduction compared to vinblastine alone.

Table 3. Percent inhibition of Alamar Blue incorporation in HCT116 cells											
		[Levobupivacaine] (μM)									
		6.160	3.080	1.540	0.770	0.385	0.193	0.096	0.048	0.024	0.000
[Vinblastine] (μM)	0.0250	85.17	84.99	84.85	85.30	84.86	84.82	84.16	84.23	84.29	82.76
	0.0125	84.37	84.62	83.73	84.01	83.53	81.00	81.63	81.99	80.95	81.83
	0.0063	89.15	84.15	87.29	87.93	85.49	85.71	76.93	79.26	78.46	80.86
	0.0031	85.50	86.91	84.20	82.57	83.49	74.73	73.17	82.84	69.78	68.95
	0.0016	85.16	83.89	80.45	73.97	75.86	70.71	68.45	73.86	63.90	59.16
	0.0008	72.96	78.03	72.84	61.74	64.17	63.91	27.15	60.44	32.53	30.33
	0.0004	42.31	32.08	21.18	12.55	6.22	14.80	16.65	12.53	15.97	16.18
	0.0002	11.97	21.08	11.42	22.38	12.13	9.38	30.03	19.17	0.05	4.53
	0.0001	20.56	24.01	14.10	10.02	6.91	9.86	8.42	7.82	0.65	3.94
	0.0000	18.56	23.47	7.27	15.12	18.16	9.20	3.01	9.30	8.77	8.00

Example 3: Antiproliferative Activity of Dibucaine and Vinblastine Against Human Colorectal Carcinoma HCT116

The results from a 2-fold dilution series of vinblastine and dibucaine combination on HCT116 cell growth are shown in Table 4. The IC_{50} of vinblastine is reduced by about half when combined with only 3.08 μM dibucaine. Vinblastine alone, at a concentration of 25 nM, maximally inhibits HCT116 cell proliferation by about 86%. In the presence of 6.16 μM dibucaine, close to maximal vinblastine inhibition is observed at concentrations as low as 3.1 nM, nearly an 8-fold reduction compared to vinblastine alone.

Table 4. Percent inhibition of Alamar Blue incorporation in HCT116 cells											
		[Dibucaine] (μM)									
		6.160	3.080	1.540	0.770	0.385	0.193	0.096	0.048	0.024	0.000
[Vinblastine] (μM)	0.0250	90.77	91.05	89.38	88.45	85.87	86.19	85.16	85.46	83.33	86.48
	0.0125	90.03	86.70	86.30	81.03	80.05	77.35	78.89	77.56	76.33	77.51
	0.0063	77.20	78.46	79.29	79.10	81.80	73.04	76.98	78.47	76.18	76.99
	0.0031	84.31	79.35	76.82	65.07	54.85	32.35	9.86	11.60	30.99	37.95
	0.0016	70.29	62.31	24.51	15.19	2.63	4.55	1.19	6.19	1.33	5.88
	0.0008	24.58	3.72	10.92	3.89	29.95	2.84	4.85	0.97	26.33	10.27
	0.0004	-3.09	2.30	-2.70	-2.15	0.47	2.17	1.30	23.35	-0.44	22.78
	0.0002	28.32	-3.02	0.11	-5.02	3.30	-2.20	-0.96	4.30	16.11	-1.53
	0.0001	-3.60	-0.46	-1.48	3.33	0.36	2.32	0.43	-0.76	2.46	5.91
	0.0000	10.11	-0.82	4.56	-0.28	17.47	-2.48	14.27	2.06	20.11	7.33

Example 4: Antiproliferative Activity of Mepivacaine and Vinblastine Against Human Colorectal Carcinoma HCT116

The results from a 2-fold dilution series of vinblastine and mepivacaine combination on HCT116 cell growth are shown in Table 5. The IC_{50} of vinblastine is reduced by about half when combined with only 3.08 μM mepivacaine. At 1.6 nM, vinblastine has no antiproliferative effect on its own, but in combination with 6.16 μM mepivacaine, inhibition of proliferation reaches about 47%, close to a 4-fold reduction in the concentration of vinblastine normally needed to achieve the IC50.

Table 5. Percent inhibition of Alamar Blue incorporation in HCT116 cells

		[Mepivacaine] (μM)									
Vinblastine] (μM)		**6.160**	**3.080**	**1.540**	**0.770**	**0.385**	**0.193**	**0.096**	**0.048**	**0.024**	**0.000**
	0.0250	89.87	89.73	86.33	87.41	87.25	84.11	84.01	85.31	84.76	89.92
	0.0125	82.37	82.86	79.09	77.60	78.18	78.76	79.40	80.04	79.44	77.78
	0.0063	78.38	72.04	76.86	82.58	71.82	70.86	69.25	70.32	73.47	63.48
	0.0031	54.39	50.91	34.46	23.73	20.52	5.86	7.73	10.53	11.56	24.09
	0.0016	47.58	24.80	7.88	-2.52	17.88	-0.32	-2.25	6.13	-1.94	2.53
	0.0008	26.08	6.46	37.87	-12.53	-1.34	2.83	34.74	-3.08	3.17	1.90
	0.0004	-4.97	-2.47	0.10	3.36	-5.75	15.58	-1.62	44.62	-3.97	-7.91
	0.0002	2.50	-0.58	33.04	-1.25	7.21	1.41	-1.52	2.27	-2.18	0.01
	0.0001	-2.75	-3.98	-10.59	-5.83	-2.80	0.59	-3.07	-1.84	6.28	-3.66
	0.0000	19.16	-0.50	26.08	11.90	9.12	16.06	30.93	42.93	24.82	10.74

Materials and Methods

The foregoing results were obtained with the following materials and methods.

Tumor Cell Culture

Human colorectal carcinoma HCT116 (ATCC# CCL-247) cells were grown at 37 ± 0.5°C and 5% CO_2 in McCoys 5A medium supplemented with 10% FBS, 2 mM glutamine, 1% penicillin, and 1% streptomycin.

Test Compounds

Vinblastine and dibucaine were obtained from Sigma Chemical Co. (St. Louis, MO). Levobupivacaine was obtained from Rosen Pharmacy (Boston, MA). Mepivacaine was obtained from Ceres Chemical Company, Inc. (White Plains, NY). Stock solutions (1000x) of each compound were prepared in DMSO and stored at -20°C. Master stock plates of 2-fold serial dilutions of individual compounds were prepared in 384-well plates. Combination matrices of test compounds were generated from these master stock plates by dilution into growth media described above. The final concentration of test compounds in the combination matrices was 10X greater than used in the assay. The combination matrices were used immediately and discarded. Vinblastine alone inhibits proliferation of HCT116 cells with an IC_{50} of about 1-10 nM.

Anti-Proliferation Assay

The anti-proliferation assays were performed in 384 well plates. Initially, 6.6 µl of 10X stock solutions from the combination matrices were added to 40 µl of culture media. The tumor cells were liberated from the culture flask using a solution of 0.25% trypsin. Cells were diluted in culture media such that 3000 cells were delivered in 20 µl of media into each assay well. Assay plates were incubated for 90-95 hours. At 37°C ± 5°C, twenty-five microliters of 20% Alamar Blue, in culture media, was added to each assay well following the incubation period. Alamar Blue metabolism was quantified

by the amount of fluorescence intensity 3.5 - 5.0 hours after addition. Quantification, using the LJL Analyst AD reader (LJL Biosystems), was taken in the middle of the well with high attenuation, a 100 msec read time, an excitation filter at 530 nm, and an emission filter at 575 nm. For some experiments, quantification was performed using a Wallac Victor^2 reader. Measurements were taken at the top of the well with stabilized energy lamp control; a 100 msec read time, an excitation filter at 530 nm, and an emission filter at 590 nm. No significant differences between plate readers were measured.

The percent inhibition (%I) for each well was calculated using the following formula:

%I = [(avg. untreated wells – treated well)/(avg. untreated wells)] x 100

The average untreated well value (avg. untreated wells) is the arithmetic mean of 40 wells from the same assay plate treated with vehicle alone. The data shown is the average of two 10x10 matrices, except mepivacaine, which is the result of one 10x10 matrix.

Other Embodiments

The anti-proliferative effect demonstrated with the tumor cell lines used herein can be similarly demonstrated using other cancer cell lines, such as A549 NSC lung carcinoma, MCF7 mammary adenocarcinoma, PA-1 ovarian teratocarcinoma, HT29 colorectal adenocarcinoma, H1299 large cell carcinoma, U-2 OS osteogenic sarcoma, U-373 MG glioblastoma, Hep-3B hepatocellular carcinoma, BT-549 mammary carcinoma, T-24 bladder cancer, C-33A cervical carcinoma, HT-3 metastatic cervical carcinoma, SiHa squamous cervical carcinoma, CaSki epidermoid cervical carcinoma, NCI-H292 mucoepidermoid lung carcinoma, NCI-2030, non small cell lung carcinoma, HeLa, epithelial cervical adenocarcinoma, KB epithelial mouth carcinoma, HT1080 epithelial fibrosarcoma, Saos-2 epithelial osteogenic sarcoma, PC3 epithelial prostate adenocarcinoma, SW480 colorectal carcinoma, CCL-228, MS-751 epidermoid cervical carcinoma, LOX IMVI

melanoma, MALME-3M melanoma, M14 melanoma, SK-MEL-2 melanoma, SK-MEL-28 melanoma, SK-MEL-5 melanoma, UACC-257 melanoma, and UACC-62 melanoma cell lines. The specificity can be tested by using cells such as NHLF lung fibroblasts, NHDF dermal fibroblasts, HMEC mammary epithelial cells, PrEC prostate epithelial cells, HRE renal epithelial cells, NHBE bronchial epithelial cells, CoSmC Colon smooth muscle cells, CoEC colon endothelial cells, NHEK epidermal keratinocytes, and bone marrow cells as control cells.

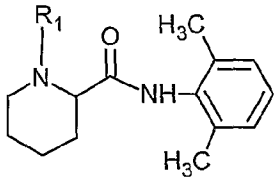
All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in oncology or related fields are intended to be within the scope of the invention.

What we claim is:

Claims

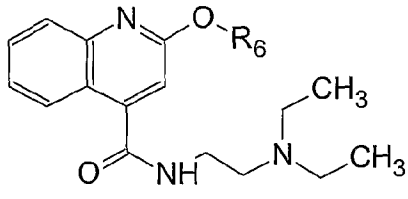
1. A method for treating a patient who has a proliferative disease, said method comprising administering to said patient:

(a) a first compound having formula (I):



(I)

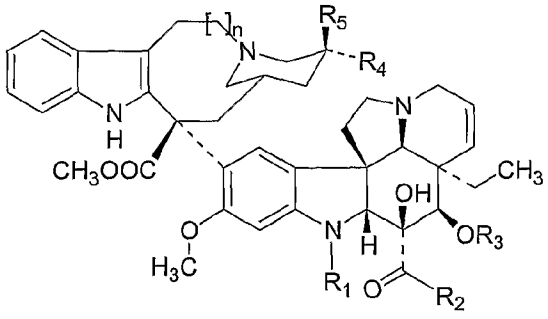
wherein R_1 is H, OH, a halide, or any branched or unbranched, substituted or unsubstituted C_{1-10} alkyl, C_{1-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} aminoalkyl, C_{1-10} alkylaminoalkyl, C_{4-10} cycloalkyl, C_{5-8} aryl, or C_{6-20} alkylaryl, or having formula (III):



(III)

where R_6 is $-((CH)_2)_2$-O-CH_3; $-((CH)_2)_2$-O-CH_2-CH_3; or $-((CH)_2)_3CH_3$; and

(b) a second compound having formula (II):



(II)

wherein R_1 is CHO, CH_3, or H, R_2 is OCH_3 or NH_2, R_3 is $OCOCH_3$ or OH, R_4 is H, CH_3, CH_2CH_3, or CF_2CH_3, R_5 is H, OH, or CH_2CH_3, and n=0 or 1, wherein said first and second compounds are administered simultaneously or within 21 days of each other, in amounts sufficient to treat said patient.

2. The method of claim 1, wherein said compound of formula (II) vinblastine, vincristine, vindestine, or vinorelbine.

3. The method of claim 1 or 2, wherein said compound of formula (I) is bupivacaine, levobupivacaine, ropivacaine, or mepivacaine.

4. The method of claim 1 or 2, wherein said compound of formula (III) is dibucaine.

5. The method of claim 1, wherein said compound of formula (I) is levobupivicaine and said compound of formula (II) is vinorelbine.

6. The method of claim 1, wherein said compound of formula (II) is dibucaine and said compound of formula (II) is vinorelbine.

7. A method for treating a disease or condition characterized by the pathological proliferation of cells, said method comprising administering to a patient in need thereof a first compound having formula (I) or formula (III) and a second compound having formula (II) in amounts effective to treat said disease or condition.

8. The method of claim 7, where the disease is cancer.

9. The method of claim 8, wherein said cancer is a cancer of the lung.

10. The method of claim 9, wherein said cancer of the lung is a non-small cell carcinoma.

11. The method of claim 8, where said cancer is colon cancer, cancer of the ovary, prostate cancer, or leukemia.

12. The method of any one of claims 7-11, wherein said compound of formula (II) is vinblastine, vincristine, vindestine, or vinorelbine.

13. The method of any one of claims 7-12, wherein said compound of formula (I) is bupivacaine, levobupivacaine, ropivacaine, or mepivacaine.

14. The method of any one of claims 7-12, wherein said compound of formula (III) is dibucaine.

15. The method of any one of claims 7-11, wherein said compound of formula (I) is levobupivicaine and said compound of formula (II) is vinorelbine.

16. The method of any one of claims 7-11, wherein said compound of formula (III) is dibucaine and said compound of formula (II) is vinorelbine.

17. The method of any one of claims 7-16, wherein said compounds are administered within 21 days of each other.

18. The method of claim 17, wherein said compounds are administered within 7 days of each other.

19. The method of claim 18, wherein said compounds are administered within 24 hours of each other.

20. The method of claim 19, wherein said compounds are administered within 1 hour of each other.

21. The method of claim 20, wherein said compounds are administered simultaneously.

22. The method of claim 21, wherein said compounds are administered in the same pharmaceutical formulation.

23. The method of any one of claims 1-22, wherein the compound of formula (I) or formula (III) is administered in an amount between 0.01 and 2000 mg per day.

24. The method of claim 23, wherein the compound of formula (I) or formula (III) is administered in an amount between 0.1 and 1000 mg per day.

25. The method of any one of claims 1-24, wherein the compound of formula (I) or formula (III) is administered topically in an amount between 0.5%-25% w/v.

26. The method of claim any one of claims 1-25, further comprising administering to said patient an antiproliferative agent listed in Table 1.

26. A composition comprising a compound having formula (I) or the formula (II) and a compound having formula (II) in amounts that, when administered to a patient having a proliferative disease, are sufficient to treat said patient.

27. The composition of claim 26, wherein said compound of formula (II) vinblastine, vincristine, vindestine, or vinorelbine.

28. The composition of claim 26 or 27, wherein said compound of formula (I) is bupivacaine, levobupivacaine, ropivacaine, or mepivacaine.

29. The composition of claim 26, wherein said compound of formula (I) is levobupivicaine and said compound of formula (II) is vinorelbine.

30. The composition of claim 26 or 27, wherein said compound of formula (III) is dibucaine.

31. The composition of claim 26, wherein said compound of formula (III) is dibucaine and said compound of formula (II) is vinorelbine.

32. A kit comprising a (i) compound having formula (I) or the formula (III), (ii) a compound having formula (II), and (iii) instructions for administering said compounds to a patient having a proliferative disease.

33. A kit comprising (i) a composition comprising a compound having formula (I) or the formula (III) and a compound having formula (II), and (ii) instructions for administering said composition to a patient having a proliferative disease.

34. A kit comprising (i) a compound having formula (I) or the formula (III) and (ii) instructions for administering said compound and a a compound having formula (II) to a patient diagnosed with a proliferative disease.

35. A kit comprising (i) a compound having formula (II) and (ii) instructions for administering said compound and a compound having formula (I) or the formula (III) to a patient having a proliferative disease.